IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Jessie L.S.- Au, *et al*.
Serial No.	:	10/807,620
Filed:	:	March 24, 2004
For:	:	METHODS AND COMPOSITIONS TO DETERMINE THE CHEMOSENSITIZING DOSE OF SURAMIN USED IN COMBINATION THERAPY
TC/AU	:	1614
Examiner	:	James D. Anderson
Attorney Docket No.	:	TNI 2-011

HONORABLE COMMISSIONER FOR PATENTS
MAIL STOP AMENDMENT
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Declarant, Jessie L.-S. Au, does declare and state that:

1. She received her Doctor of Pharmacy and Doctor of Philosophy degrees from the University of California San Francisco, in 1972 and 1980, respectively. She has been on the faculty of The Ohio State University since 1983, rising to the rank of Full Professor in 1992. She was Co-director of three research programs (Developmental Therapeutics, Urologic Oncology, Head and Neck Oncology), Director of Translational Research, and Deputy Director, of The Ohio State University Comprehensive Cancer Center, one of the then 28 centers in the U.S. that received such designation from the National Cancer Institute. She has served on multiple government advisory boards (including, inter alia, Experimental Therapeutic Study Section, Pharmacology Study Section and Board of Scientific Counselors of the National Institutes of Health, U.S. Army Breast Cancer Program, Cancer Center Support Grant Review Committee, Manpower Initial Review of the National Cancer Institute, Clinical Studies Initial Review Committee for the National Cancer Institute, Developmental Therapeutics Study Section of Oncological Sciences Initial Review Group of the National Institutes of Health). She is also on the Editorial Boards of Pharmaceutical Research and The AAPS Journal. She received a Research Career Development Award and a Merit Award from the National Cancer Institute; and a Distinguished Scholar Award, the Dorothy M. Davis Chair in

Cancer Research and a Distinguished University Professorship from The Ohio State University; and a Research Achievement Award from the American Association of Pharmaceutical Scientists. She is a Fellow of the American Association of Advancement of Science and a Fellow of the American Association of Pharmaceutical Scientists. She is a member of the US Food and Drug Administration Pharmaceutical Sciences Advisory Committee.

2. Her research interests and experience are to develop effective cancer chemotherapy, by identifying effective drugs or combinations of drugs, by identifying the optimal treatment schedules including the dose and treatment duration, and by improving the delivery of drugs to tumors. Her work in these areas has led to the identification of a new treatment for bladder cancer, for which she has received U.S. Patent No. 6,286,513 B1. This new bladder cancer treatment is based on a new treatment schedule using mitomycin C, a drug that has been used for over 25 years. She and her co-inventor discovered that the prior regimen of administering mitomycin C was less than optimal and subsequently found a new treatment regimen that is nearly twice as effective in human patients, as compared to the prior regimen. The new treatment regimen requires careful adherence to a precise treatment protocol aiming to: (1) reduce the volume of urine in the bladder of the patient, (2) minimize the volume of the solution that is instilled in the bladder, (3) reduce the rate of urine production by the patient, and (4) alkalinize the urine of the patient. Deviations from this protocol will result in less effective treatment. For this reason, treating physicians frequently request detailed instructions for the practical application of the treatment regimen. This is because the treating physicians understand that without detailed instructions the desired treatment results will not be obtained. In other words, absent the instructions the effective treatment does not exist.

3. She is a co-applicant for the instant application, describing methods and compositions for using very low and nontoxic doses of suramin to improve the activity of other chemotherapeutic agents (referred to as sensitizer) in patients. These methods and compositions include, *inter alia*, the suramin dosing nomogram.

4. The suramin dosing nomogram is needed to ascertain that suramin is used effectively. This is because of the following reasons.

   (a) As explained in greater detail in the application, suramin has been evaluated during the 1980s and 1990s for its antitumor activity in extensive preclinical studies and in over 30 clinical trials where suramin was administered at doses that would achieve plasma concentrations in excess of 100 μM. Taken together,

these studies showed that high doses of suramin did not enhance the efficacy and only enhanced the toxicity of chemotherapy. The U.S. Food and Drug Administration disapproved high dose suramin as a new drug (Kaur, *Invest New Drugs*, 20, 209, 2002). Dr. Au and collaborators discovered that suramin can enhance the effect of cancer chemotherapy against tumors, and that this suramin effect displays an unusual and counter-intuitive dose-effect relationship, in that it occurs only at lower suramin concentrations between about 10 to about 50 μM and is lost at higher concentrations. Dr. Au and her co-inventor were awarded U.S. Patent No. 6,599,912B1 for the use of low and nontoxic suramin as a sensitizer.

(b) Because the effectiveness of suramin is limited to low concentrations and is lost at higher concentrations, clinical application is only practical and achievable if there is a method to identify the proper suramin dose that yields the desired narrow range of concentrations.

(c) As explained in greater detail in the application, suramin is an effective sensitizer for all tested chemotherapeutics. This effect occurs at an extracellular, *e.g.*, plasma, concentration range between 10 and 50 μM. The effective suramin concentration should be present **while** the chemotherapeutic also is present in the body at an active concentration. It is generally known that nearly most of an administered drug is eliminated after three half-lives and that most chemotherapeutic agents have a half-life of about or less than 16 hours. Accordingly, the use of suramin as a sensitizer requires that its concentrations are maintained in the effective range for 48 hours (*i.e.*, 3 times 16 hours).

(d) For most drugs, choosing the proper dose is a relatively routine and easy task. For example, most chemotherapy agents are given at a fixed frequency and most agents are given at a fixed dose. The latter is because most agents have plasma half-lives of several hours and are completely eliminated from the body within days and, therefore, will not show significant accumulation in the body by the time the next dose is administered, usually in 7 or 21 days. However, this general practice does not apply to suramin, because of its unusual pharmacokinetic behaviors, as follows. First, Dr. Au and collaborators found a substantial inter-subject variability (180%) in the disposition of low and nontoxic doses of suramin in cancer patients, which indicates that administration of the same dose of suramin will not result in the same, desired plasma concentration

in all patients. In fact, different patients require doses of up to 5-fold different size in order to maintain the plasma concentrations in the desired range (Chen, *Pharm. Res.*, 23, 1265, 2006). Second, suramin has an unusually slow elimination from the body, as signified by the unusually long plasma half-life of about 10 days (Chen, 2006). The long half-life indicates that a significant fraction of the suramin dose remains in the body at the time of the subsequent treatment. For example, a patient with a half-life of 10 days will have approximately 25% of the dose remaining in 20 days. Third, unexpected changes in treatment frequency or time intervals between treatment cycles are a fairly common occurrence in cancer chemotherapy. For example, patient toxicity such as low blood cell counts may mandate treatment delay, and practical issues such as availability of transportation or schedule feasibility (both for patients or treating physicians) may also alter the treatment intervals. These unexpected changes, in turn, introduce the uncertainty on the eliminated amount of the drug dose from the previous treatment and, therefore, the uncertainty of finding the proper dose for the patient. The long half-life, coupled with the frequent, unexpected changes in treatment frequency and intervals, make it difficult to find the proper effective suramin dose, in order to satisfy the requirement of maintaining the drug concentrations within a narrow range. For example, if the dose in the subsequent treatment is higher than necessary to replace the amount that has been eliminated, drug accumulation will occur and will cause the plasma concentrations to increase, *e.g.*, to levels where suramin is not effective. Conversely, if the dose in the subsequent treatment is insufficient to replace the eliminated amount, the patient will not receive sufficient drug.

(e) The above considerations indicate the need of a method or composition to take into account the various patient characteristics and the timing of the next treatment relative to the previous treatment, so that the patient is given the proper dose of suramin. The proper dose is the one that yields the effective concentrations (10-50 μM) and does not yield the higher concentrations that are known to be ineffective.

5. Development of an effective method of administering suramin required extensive research and development in human patients. Dr. Au and collaborators evaluated several methods. Initial studies used real time pharmacokinetics together with computer simulations to determine the correct dose. Real time pharmacokinetics means that

blood samples were taken from patients to determine the plasma concentrations of suramin at a specific time, usually a day before the scheduled treatment, so that the drug dose needed to bring the concentrations to the desired levels could be calculated. These initial methods were found to be sufficient to yield and maintain the desired suramin concentrations for 48 hours. However, these methods can only be applied in a limited number of medical centers that have these highly specialized research capabilities and, therefore, are not applicable to the general public. Different dosing schedules also were evaluated. This included administering suramin in split doses with two-thirds of the total dose given immediately before administration of the cancer chemotherapeutics used in combination with suramin, followed by the remaining one-third of the dose given 24 hours later. This method also yielded and maintained the desired suramin concentrations for 48 hours. But it also had the practical problem of needing a longer hospital stay for the patient and increasing the treatment costs, which may limit the general applicability of suramin. Further studies evaluated the required dose size as a function of patient characteristics; the initial results in a small number of patients suggested that the dose was affected by the squared value of the patient's body surface area and the patient gender (Chen, 2006). Several other potential correlates were evaluated, but were found to be insignificant predictors. An example of an insignificant predictor is kidney function, measured as glomerular filtration rate. This parameter is of primary importance in dosage calculations for other drugs, including platinum compounds (Calvert, *J. Clin. Oncol.*, 7, 1748, 1989), and it was surprising to find that it was of minimal relevance to suramin dose prediction. Further study in additional patients revealed that the effect of gender was relatively small and could be ignored. These results were further used with computer simulations to calculate the dose based on the time elapsed since the previous treatment. This was necessary to accommodate the unforeseen delay or other changes in treatment frequency. The composite findings were used to develop the suramin dosing nomogram described in the instant application. The nomogram was found to be successful in finding the proper suramin dose to maintain the desired plasma concentrations in 94% of treatments (Chen, 2006).

6. The dosing nomogram enables a health care professional, such as a pharmacist or a physician, to calculate the suramin dose for a patient using the squared value of the patient's body surface area and the time elapsed since the previous treatment. This

dosing nomogram is the only known method that is sufficiently practical for clinical application, yet sufficiently accurate to achieve the desired plasma concentrations.

7. Absent the dosing nomogram, it will not be possible to calculate the proper suramin dose for a patient and the patient cannot be treated with suramin. As has been discussed in the example of mitomycin C treatment for superficial bladder cancer, it is of great importance to the treating physician and to the pharmacist who prepares the drug dose, to know what exactly needs to be done. For this reason, it is imperative to supply the dosing nomogram together with the drug for clinical treatment of the patient.

8. Alternative methods to determine the needed suramin dose, for example real-time pharmacokinetic monitoring of patient plasma concentrations, are not practical and do not enable the clinical use of suramin in the general population. In other words, the ability to use suramin as a sensitizer in patients relies on using the method of dose calculation or nomogram presented in the instant application.

9. Dr. Au and her collaborators developed the method of dose calculation based on the study of the pharmacokinetics of suramin in patients. Consequently, the method of dose calculation could not exist in the absence of the drug suramin.

10. Based on the foregoing, she comes to the inescapable conclusion that the methods of dose calculation or nomogram cannot exist without suramin, and that suramin cannot exist without the nomogram.

11. All statements made herein of her own knowledge are true and all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

FURTHER DECLARANT SAYETH NAUGHT.

Date: 3/6/08

Jessie L.-S. Au